REMARKS

Withdrawn Rejections

Applicant acknowledges that the following rejections are withdrawn by the Examiner:

The rejection of claims 2, 12, 15, 16, 20, 26, 43, 51, and 54 under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 1, 2, 8, 15, 31, and 37 under 35 U.S.C. 102(b) as being anticipated by Bona et al. (U.S. Patent 5,969,109).

The rejection of claims 1, 2, 8, 15, 31, 37, and 54 under 35 U.S.C. 102(e) as being anticipated by Papadimitriou (U.S. 20021/0037841 Al).

The rejection of claims 1-5, 8, 12, 15, 31, 37, 40, and 54 under 35 U.S.C. 102(e) as being anticipated by Finn et al. (U.S. 2003/0171285 Al; Effective filing date = November 20, 2001).

Oath and Declaration

Applicant acknowledges that a new Oath or Declaration correctly identifying the application by its US serial number is required and will provide a new Declaration in due course. Applicant has experienced delays in locating and receiving signature from inventors whom have since left the company.

Specification

In **points 9 &10** the Examiner objected to the specification because typographical errors in the cross-reference to related application section of the specification.

Applicant has amended the cross-reference to related application section to correct the errors.

In **point 11** the Examiner objected to the specification because in Example 1, at Paragraph [0457], the specification identifies, U.S. application interim serial no. P-107,891 rather than U.S. Serial Number 10/662,884, which was filed on 9/16/2003.

Applicants have amended Paragraph [0457] as suggested by the Examiner.

Claim Rejections - 35 USC § 103

The Examiner rejected Claims 1-5, 8, 12, 15-17, 20, 23, 26, 31, 34, 37, 40, 43, 51, 54, and 205-217 under 35 U.S.C. 103(a) as being allegedly unpatentable over Olson et al. (Chapter 12. Preparation and Characterization of Poly(ethylene glycol)ylated Human Growth Hormone Antagonist: (1997)) in view of Pharmacia Fine Chemicals (Chapter 2. Ion Exchange Chromatography Principles and Methods. Pharmacia Fine Chemicals: (1980)).

The Examiner argues Olson et al, describes the pegylation of Growth Hormone Antagonist (GHA) with succinimidyl ester of carboxymethylated methoxy-PEG or the succinimidyl ester of propionic acid of methoxy-PEG. Approximately an equal molar amount of PEG5000 reagent for each potential reactive site was found to be optimal. A protein concentration of 10 mg/m was used in 50 mM sodium phosphate, pH 7.5. The components were mixed and incubated at room temperature for approximately one hour. Olson et al. describes the use of Phenyl Toyopearl 650M as a hydrophobic interaction chromatography step. The preparation was loaded at a protein concentration of up to 3.7 grams per liter of resin. The main protein peak was pooled and desalted by either G-25 Sephadex or by diafiltration (see pages 171-173, Experimental, PEG Derivatization Column Chromatography sections). The Examiner asserts that Olson et al. (*it is noted that the Applicant believes that the Examiner intended to refer to* "Pharmacia Fine

Chemicals (Chapter 2. Ion Exchange Chromatography Principles and Methods") describes the optimization amphoteric samples by selecting the appropriate pH" (see page 29, section 7.1 Choice of ion exchanger matrix).

The Examiner avows that one of ordinary skill in the art would have expected to succeed in altering the ionic charge on pegylated GHA, because Olson et al, describes the alteration of ionic association with a cationic-exchange resin due to a reduction in the number of primary amino groups due to pegylation. Furthermore, it would have been obvious to one of skill in the art to alter the ionic association resin by adjusting the pH of the buffer thereby affecting the net charge of PEGylated GHA and favoring the ability to bind an anion exchange resin.

The Examiner concludes it would have been obvious to the person having ordinary skill in the art to fractionate the PEGylated GHA using an anion exchange chromatography resin in place of the cation exchange resin described by Olson et al. by adjusting to the appropriate pH as suggested by techniques known in the art as discussed by the Pharmacia chapter (current application, claims 1-5, 8, 12, 15-17, 20, 23, 26, 31,34,37,40,43, 51, 54, and 205-217).

Applicant respectfully submits that the Office has failed to establish a *prima facie* case of Obviousness.

As stated by the Board of Patent Appeals and Interference in *Ex parte Levengood,* 28 U.S.P.Q.2d 1300 (1993):

> *At best, the Examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard of obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness.*

Furthermore, it is respectfully submitted that the Examiner has failed to show that every element of the claimed invention is allegedly disclosed by the prior art.

As described in Olson et al. the purification of a PEGylated growth hormone antagonist by a cation exchange column requires that the column be run at a **low pH** (pH 4 – according to Olson et al.). The low pH is required to achieve separation of the different PEGylated isoforms based on the charge differential of the different PEG isoforms. Applicant also draws the Examiner's attention to Fig. 17 (page 29) of "Pharmacia Fine Chemicals Chapter 2. Ion Exchange Chromatography Principles and Methods", which also teaches that a low pH is used to purify amphoteric samples by cation exchange chromatography.

However, purification of the PEGylated growth hormone antagonist by cation exchange chromatography under the required conditions results in an unacceptably high level of aggregate (~20%). Such aggregation levels as part of a viable commercial process are impractical.

Surprisingly, it was found that when the growth hormone antagonist was purified by anion exchange chromatography at preferably pH 7 the PEG isoforms could be separated but **aggregates were not formed**. The problem of aggregation of the PEGylated growth hormone antagonist when purified by cation exchange chromatography and the instantly claimed solution of purification of the PEGylated growth hormone antagonist by anion exchange chromatography and the reduction in aggregate is neither taught or disclosed by Olson et al. and "Pharmacia Fine Chemicals Chapter 2. Ion Exchange Chromatography Principles and Methods".

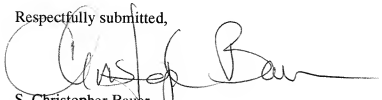
Therefore, the instantly claimed invention is nonobvious over Olson et al. and "Pharmacia Fine Chemicals Chapter 2. Ion Exchange Chromatography Principles and Methods".

Conclusion

Claims 1-5, 8, 12, 15-17, 20, 23, 26, 31, 34, 37, 40, 43, 51, 54 & 205-217 are pending. No new matter has been added.

In view of the foregoing, it is respectfully submitted that all claims now pending in the present application are in condition for allowance. Therefore, swift passage of the application and claims to issue is respectfully requested.

Respectfully submitted,



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